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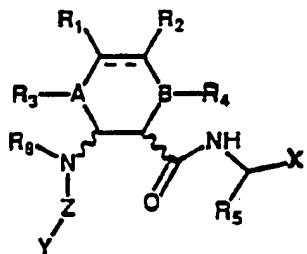
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(71) Applicants (for all designated States except US):	A. MENARINI INDUSTRIE FARMACEUTICHE RIUNITE S.R.L. [IT/IT]; Via Sette Santi, 3, I-50131 Florence (IT). MALESCI ISTITUTO FARMACOBIOLOGICO S.P.A. [IT/IT]; Via Porpora, 22/24, I-50144 Florence (IT).	Published <i>With international search report.</i>
(72) Inventors; and		
(75) Inventors/Applicants (for US only):	SISTO, Alessandro [IT/IT]; Via Proba Petronia, 43, I-00136 Rome (IT). FINCHAM, Christopher [GB/IT]; Via Don Luigi Sturzo, 28, I-00040 Pomezia (IT). POTIER, Edoardo [IT/IT]; Viale dei Salesiani, 82, I-00175 Rome (IT). MANZINI, Stefano [IT/IT]; Via della Mattonaia, 25, I-50121 Florence (IT). ARCAMONE, Federico [IT/IT]; Via 4 Novembre, 26, I-20014 Nerviano (IT). LOMBARDI, Paolo [IT/IT]; 16a Strada, 22, I-20020 Cesate (IT).	
(74) Agent:	GERVASI, Gemma; Notarbartolo & Gervasi S.r.l., Viale Bianca Maria, 33, I-20122 Milano (IT).	

(54) Title: TACHYKININ ANTAGONISTS



(57) Abstract

A description is given of tachykinin receptor antagonists having general formula (I); their preparation and use in pharmaceutical formulations.

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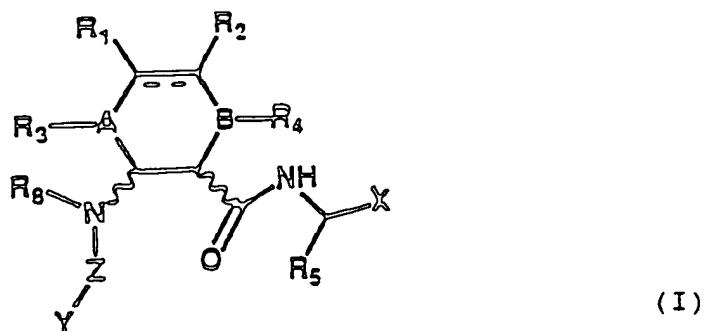
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TACHYKININ ANTAGONISTS

Field of the invention

The present invention refers to tachykinin antagonists, their preparation
5 and use in pharmaceutical formulations.

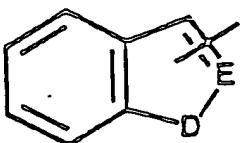
In particular, the present invention refers to compounds having general
formula (I)



wherein:

Y is selected out of a group consisting of an aryl-, aryl-alkyl-, alkyl-
10 aryl- radical containing 7 to 12 carbon atoms, whose aromatic ring
possibly contains an heteroatom selected from the group N, O, S, and
wherein the aromatic ring is unsubstituted or substituted with one or
more substituent(s) selected from a group consisting of halogen, a linear
or branched alkyl radical containing 1 to 6 carbon atoms, possibly
15 substituted with not more than three fluorine atoms, a linear or branched
oxyalkyl radical containing not more than three fluorine atoms, -NH₂, -
NHR₁₁, -N(R₁₁)₂, -CONHR₁₁, -COR₁₁, -COOR₁₁, -R₁₂COOR₁₁, -CONHR₁₁, -
R₁₂CONHR₁₁, -NHCOR₁₁, -NHCOOR₁₁, -R₁₂COOR₁₁, nitro, wherein R₁₁ and R₁₂
are independently selected from H, a linear or branched alkyl radical
20 containing 1 to 6 carbon atoms, a radical of type

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wherein D stands for O, S, CH₂, N-R₉ where R₉ is selected from a group consisting of H, a linear or branched alkyl radical containing 1 to 6 carbon atoms, acyl radical R₁₀-CO wherein R₁₀ is selected from H, a linear or branched alkyl radical containing 1 to 3 carbon atoms and E =

5 CH or N, each with suitable substituents;

Z is selected from the group consisting of CH₂ and CO;

R₈ is selected from a group consisting of H, a linear or branched alkyl radical containing 1 to 6 carbon atoms;

symbol — represents a single or a double bond: if the bond is single,

10 R₁ and R₂ are selected out of a group consisting of hydrogen, hydroxyl, methoxy-ethoxy-ethoxyl or methoxy-ethoxy-methoxyl, and halogen or are joined to form an epoxide; if the bond is double, they are hydrogen or halogen; A and B stand for N or CH; R₃ and R₄ are selected out of the group consisting of hydrogen, a linear or branched alkyl radical

15 containing 1 to 6 carbon atoms, or are joined together to form a -(CH₂)_n-bridge, where n stands for a whole number from 1 to 3;

R₅ is selected out of a group consisting of an aryl-, aryl-alkyl-, alkyl-aryl- radical containing up to 15 carbon atoms, whose aromatic ring possibly contains an heteroatom selected from the group N, O, S, and

20 wherein the aromatic ring is unsubstituted or substituted with one or more substituent(s) selected from a group consisting of halogen, a linear or branched alkyl radical containing 1 to 6 carbon atoms, possibly

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substituted with not more than three fluorine atoms, a linear or branched oxyalkyl radical containing not more than three fluorine atoms, -NH₂, -NHR₁₁, -N(R₁₁)₂, -CONHR₁₁, -COR₁₁, -COOR₁₁, -R₁₂COOR₁₁, -CONHR₁₁, -R₁₂CONHR₁₁, -NHCOR₁₁, -NHCOOR₁₁, -R₁₂COOR₁₁, nitro, wherein R₁₁ and R₁₂ are as defined above;

X is selected from a group consisting of COOR₆, -CH₂OR₆, -NR₇COR₆, -NR₆COOR₇, -CONR₆R₇, R₆ and R₇ are independently selected out of a group consisting of an aryl-, aryl-alkyl-, alkyl-aryl- radical containing up to 15 carbon atoms, whose aromatic ring possibly contains an heteroatom selected from the group N, O, S, and wherein the aromatic ring is unsubstituted or substituted with one or more substituent(s) selected from a group consisting of halogen, a linear or branched alkyl radical containing 1 to 6 carbon atoms, possibly substituted with not more than three fluorine atoms, a linear or branched oxyalkyl radical containing not more than three fluorine atoms, -NH₂, -NHR₁₁, -N(R₁₁)₂, -CONHR₁₁, -COR₁₁, -COOR₁₁, -R₁₂COOR₁₁, -CONHR₁₁, -R₁₂CONHR₁₁, -NHCOR₁₁, -NHCOOR₁₁, -R₁₂COOR₁₁, nitro, wherein R₁₁ and R₁₂ are as defined above, with the proviso that if X= -CONR₆R₇ then Z is other than C0 or R₈ is other than H.

Symbol means that the configuration of those asymmetric carbon atoms of 2-amino-cyclohexanecarboxylic acid could be either S or R, with the proviso that such configuration can not be S or R for both the asymmetric carbon atoms (the two substituents must be cis).

Tachykinin antagonist compounds as per formula (I) prove to be effective in the treatment of diseases where tachykinins play a pathogenic role, in particular in the treatment of arthritis, asthma, inflammations, tumoral growth, gastrointestinal hypermotility, Huntington's disease, neuritis, neuralgia, migraine, hypertension, incontinence of urine, urticaria,

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carcinoid syndrome symptoms, influenza, and cold, disorders related to immune system.

State of the art

Tachykinines are a family of three peptides at least, known as substance

5 P (SP), Neurokinin A (NKA) and Neurokinin B (NKB).

Research in the field of tachykinin antagonists, initially directed toward single or multiple replacement of amino acids of the peptide agonists sequence of Substance P and of the other tachykinins, brought to the discovery of nonapeptides containing one or more D-tryptophan units
10 [Regoli et al., Pharmacol., 28, 301 (1984)].

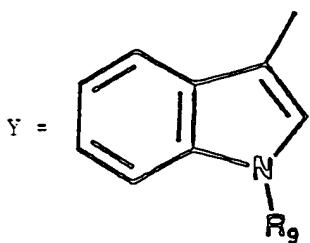
On the other hand, the problems related to the use of high-molecular-weight peptides as drugs (multiplicity of enzymatic hydrolytic attack sites, poor bioavailability, rapid excretion from the liver and kidneys) spurred to search for the minimum peptide fragment still capable of
15 exerting an antagonist action. These studies brought to the singling out of suitably derivatized SP antagonists tripeptides and dipeptides (European patents Nos. 333174 and 394989). Recently it has been reported a new class of tachykinin receptor antagonists, not containing natural
AMINO ACIDS, and then expected to be more stable from a metabolic point
20 of view (PCT Application N° WO 94/13694).

Detailed description of the invention

It has surprisingly been found - and this finding constitutes a fundamental feature of the present invention - that non-peptidic compounds of general formula (I) as defined above are good inhibitors of
25 the tachykinins bond to NK1 receptor and have a sufficient metabolic stability.

A preferred group of compounds under the present invention includes compounds of formula (I) wherein:

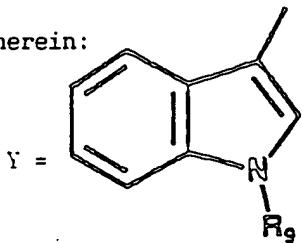
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and Z = CO, R8 = H, X = NR7COR6 and R1, R2, R3, R4, R5, R6, R7, R9, R10, R11, A, and B are as defined above.

Particularly preferred products are compounds of general formula (I)

wherein:



5 and Z = CO, R8 = H, R5 = 2-methylnaphthyl X = NR7COR6, R6 = benzyl, R7 = methyl and the other substituents are as defined above.

The present description sets forth the following substituent groups as particularly preferred:

the alkyl radical is selected out of a group consisting of methyl, ethyl, 10 propyl, butyl, and pentyl; possibly substituted aryl-, alkyl-aryl- and aryl-alkyl- radicals present preferably an alkyl radical as defined above, while the aryl moiety is preferably possibly substituted pyridine, benzofuran, biphenyl benzene, indole, naphthyl, tetrahydroquinoline, imidazole, tetrahydroindoline, thienyl, furan, thiophene, indan; a 15 cycloalkyl radical, possibly substituted at least with an atom selected out of a group consisting of N, S and O, is preferably selected out of a group consisting of cyclohexane, cyclopentane, cycloheptane, cyclooctane, piperidine, morpholine, piperazine, and pyrazine, halogen, as used herein, means fluoro chloro, bromo and iodo.

20 In view of the asymmetry centres of formula (I), this invention refers to the various diastereoisomers of said formula; in particular, substituent

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R₅ is preferably in S-position and the amino and carboxy groups on the cyclohexane unit can assume the (1R,2S) and (1S,2R) configuration.

The compounds under the present invention proved to be SP, Neurokinin A, and Neurokinin B receptor antagonists. Therefore, they can be utilised

5 for the prevention and treatment of diseases where tachykinins (SP, NKA, NKB) play a neuromodulating role, such as respiratory conditions (e.g. asthma, allergic rhinitis) [Peters et al Amer.Rev.Resp.Dis.145,A 835 (1992)], ophthalmic conditions (e.g. conjunctivitis), cutaneous conditions (e.g. allergic dermatitis, dermatitis by contact, psoriasis)

10 [Hamelet et al, Can. J. Pharm. Physiol. 66,1361 (1988)], intestinal conditions (e.g. ulcerative colitis, Crohn's disease)[Mantyh et al, Proc.Natl. Acad.Sci.U.S.A.85,3235 (1988)].

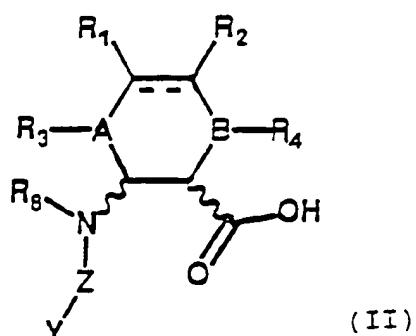
The present invention referred to pharmaceutical compositions containing as active ingredient a compound of general formula (I) in admixture with 15 an organic or inorganic pharmaceutically acceptable carrier. The suitable carriers include substances usually employed in manufacturing preparation as inert diluents, lubricants, dispersing and surface active agents, aqueous, oil or glycolic suspensions. Such compositions, prepared following known procedures, consisted pills, tablets, pellets, solutions, 20 suspension emulsion, suppositories, and may be administered orally, topically, rectally parenterally and as retard form.

An appropriate dosage level will generally be about 0.04 to 40 mg per Kg patient body weight per day and may be administered on a regimen of 1 to 3 times per day.

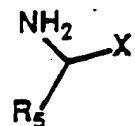
25 Another fundamental object of the invention is the preparation of compounds of general formula (I) by condensation.

Compounds of general formula (I) as defined are prepared condensing, in the presence of a suitable condensing agent, intermediate of formula (II)

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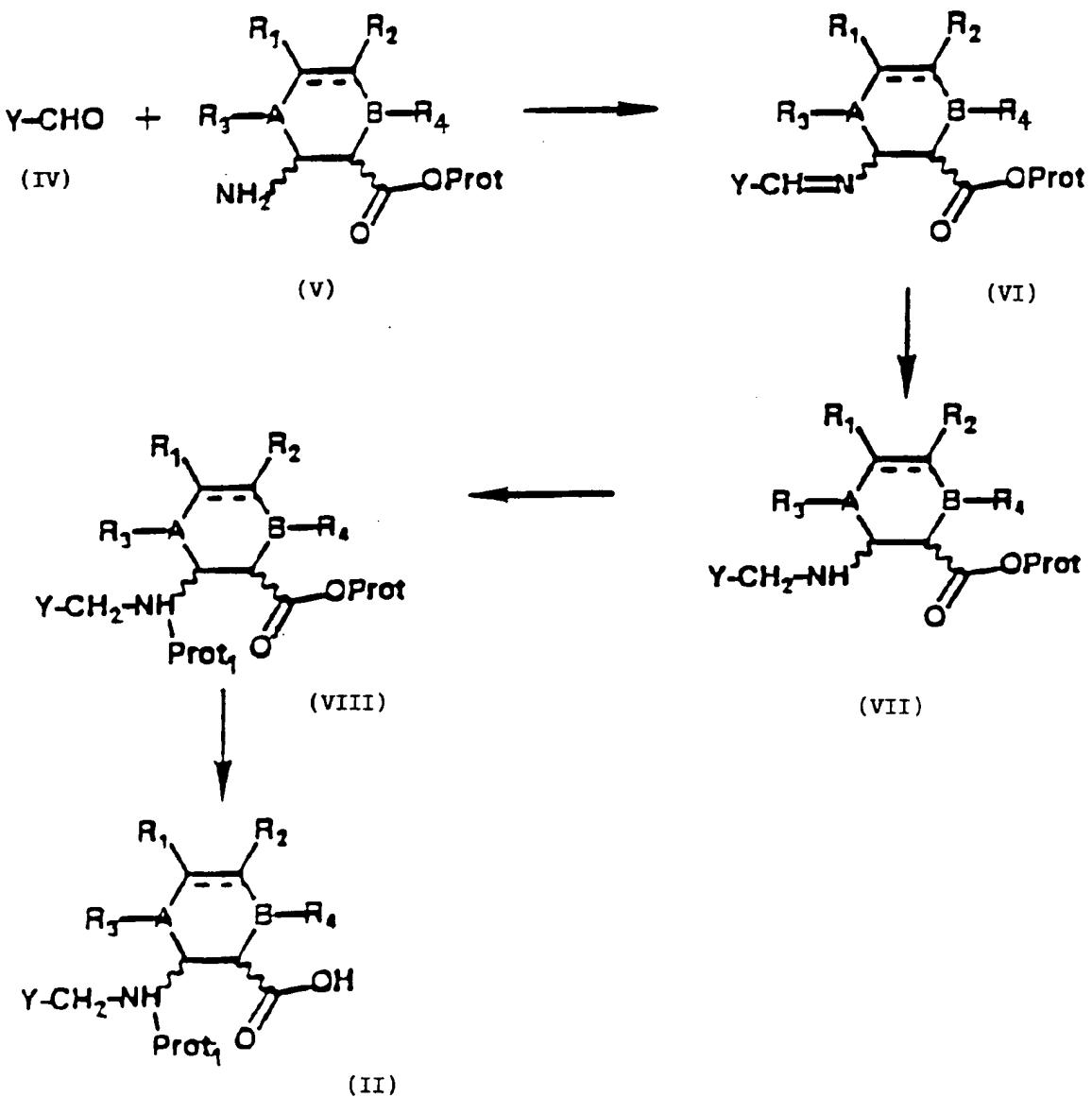
with intermediate of formula (III)



where R1, R2, R3, R4, R5, R8, Y, Z, X, A and B are as defined above,
said compound of formula (II), wherein Z= CH₂, R8= H, being prepared
following the synthetic scheme (1) below reported.

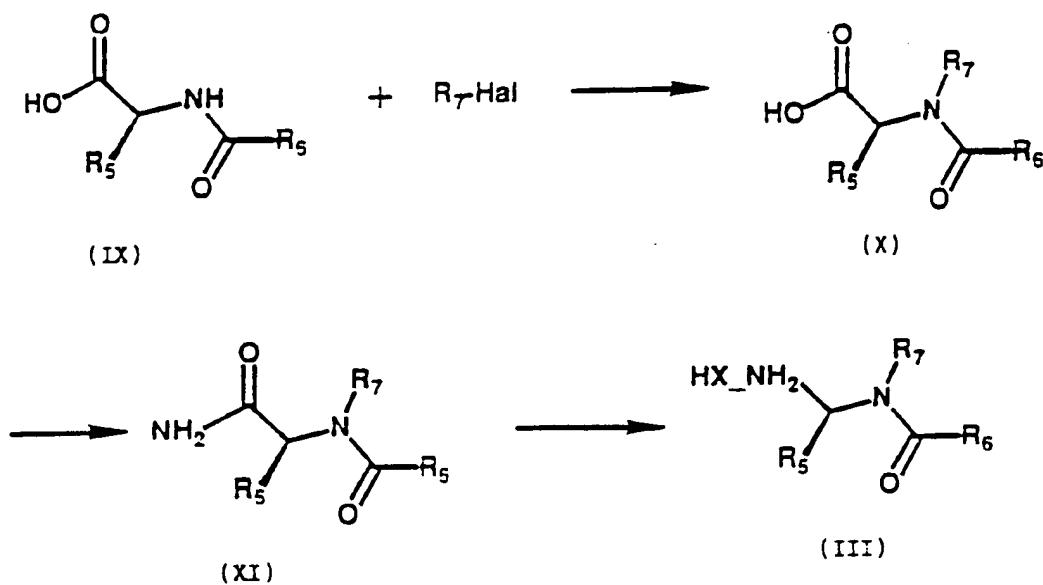
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Scheme 1



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The synthetic scheme 2



illustrates the preparation of an intermediate of formula (III), where $X = \text{NR}_7\text{COR}_6$ and the configuration of the carbon atom linked to R_5 is preferably S. said compound being prepared by reaction between the D-aminoacid derivative of formula (IX). commercially available or

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synthesised as described in the examples or through synthetic routes obvious for those skilled in the art, and the requisite alkyl halide of general formula R₇-Hal, wherein Hal is selected from the group consisting of chloro, iodo and bromo and R₇ is as defined above, in presence of a 5 active hydride reagents in aprotic polar solvent as dioxane or tetrahydrofuran. Preferably the reaction is carried out at 0° C in tetrahydrofuran employing as a base sodium hydride and as alkylating agent methyl iodide. The following reaction with N-hydroxybenzotriazole ammonium salt in presence of a suitable condensing agent, produces the 10 corresponding amide and, by treatment with bis(trifluoroacetoxy)iodobenzene, to the gem-diamine derivate (III). The crude product is purified by chromatography or crystallisation.

Excellent product yield and purity were obtained using benzotriazolyloxy tripyrrolidine phosphonium hexafluorophosphate (PyBOP) as a condensing 15 agent. In particular, the reaction was carried out by addition of slight excess of PyBOP to a carboxylic component (formula II) solution, maintained at low temperature, followed by addition of the aminic component hydrochloride (formula VI) and a quantity of tertiary amine of three equivalents in respect of the condensing agent.

20 An alternative procedure envisages the use, as a condensing agent, of 1-ethyl-3-(3'-dimethylaminopropyl)-carbodiimide (WSC, HCl).

The compounds of this invention can exist in different isomeric configurations. In fact, the configuration of the carbon atom bound to substituent R₅ is univocally determined by the synthesis starting

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compound being of formula VI. However, the other starting compound (i.e. 2-aminocyclohexanecarboxylic acid as per formula II) has 2 asymmetric carbon atoms and usually consists of an inseparable mixture of two enantiomers, whose ring substituents are cis. It follows that the 5 compounds of this invention are mixtures of diastereoisomers. Said mixtures can be easily resolved by chromatography. In any case, compounds of formula (I) can be used both in optically active form and in the form of isomeric mixtures.

The following examples illustrate some embodiments of the claimed 10 invention and the synthesis procedure thereof.

EXAMPLE 1

benzyl ester of $N^{\alpha}\text{-}(\text{[N(1(H)indol-3-yl-carbonyl)(1R,2S)-2-aminocyclohexan carbonyl]-L-phenylalanine}$ and benzyl ester of $N^{\alpha}\text{-}(\text{[1(H)N(indol-3-yl-carbonyl) (1S,2R)-2-aminocyclohexancarbonyl]-L-phenylalanine}$

15 1a) WSC.HCl (89 mg, 0.46 mmol) was added to a chilled solution of cis N-(1(H)indol-3-yl-carbonyl)-2-aminocyclohexanecarboxylic acid (prepared as described in WO-94/013694) (111 mg, 0.388 mmol) and N-hydroxybenzotriazole (HOEt) (76 mg, 0.50 mmol) in CH₂C₁₂ (1 ml)/dimethylformamide (DMF) (0.5 ml). The solution was stirred at 0°C for 20 min., then hydrochloride of L-phenylalanine benzyl ester (150 mg, 0.514 mmol) was added, followed by dropwise addition of diisopropylethylamine (to pH 9). The resulting solution was stirred at 0°C for 30 min. then at room temp. for 72h. The CH₂C₁₂ was removed in vacuo, the residue treated with H₂O (30 ml), and the emulsion extracted 25 with diethyl ether (1 x 200 ml). The layers were separated, and the organic phase washed with 1N HCl (2 x 50 ml), H₂O, 5% NaHC₃O₃ (2 x 50 ml), H₂O and brine, then dried (Na₂SO₄), filtered and the filtrate concentrated in vacuo. The two diastereoisomers were separated by

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reversed-phase on a 7 μ Lichrosorb R RP-18 column (Hibar Merck R) eluting with:

A = 0.1% trifluoroacetic acid in acetonitrile;

B = 0.1% trifluoroacetic acid in water;

gradient of 45% to 25% of A over 2h;

5 flow rate 9 ml/min; effluent monitored at 230 nm (UV detector).

The fractions corresponding to the two peaks of the two isolated diastereoisomers were joined, concentrated to small volume at a reduced pressure and repeatedly freeze-dried, giving 59 mg. (30% yield) and 64.2 mg. (32% yield) of the two diastereoisomers.

10 HPLC analysis on a Phase Separation Spherisorb ODS-2 5 46X250 mm column under isocratic conditions at 35% of A, flow 1ml/min, showed a single peak for each of the two products (denominated "fast" and "slow" depending on their being eluted at an earlier or, respectively, at a later time):

15 HPLC (fast) = 9.34 min HPLC (slow) = 10.02 min

EXAMPLE 2

1-{N-(1(H)indol-3-yl-carbonyl)(1R,2S)-2-aminocyclohexanecarbonyl}-amino-
1-(phenylacetyl)amino-2-phenyl-ethane and 1-{N-(1(H)indol-3-yl-
carbonyl)(1S,2R)-2-aminocyclohexanecarbonyl}-amino-1-(phenylacetyl)amino-

20 2-phenyl-ethane

2a) Dicyclohexylcarbodiimide (348 mg, 1.69 mmol) was added to a chilled solution of Boc-L-phenylalanine (387 mg, 1.46 mmol) and the ammonium salt of 1-hydroxybenzotriazole (248 mg, 1.63 mmol) in DMF (5 ml). The solution was stirred at 0°C for 90 min, then at room temperature for 2h. The 25 reaction mixture was filtered, and the filtrate poured into water (77 ml). The emulsion was extracted with diethylether (1 x 200 ml), the layers separated, and the organic phase washed with 5% NaHCO₃, water and

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brine, then dried (sodium sulphate), filtered, and the filtrate concentrated in vacuo to give Boc-L-phenylalanine amide (370 mg. 96%). Analytical HPLC in the condition of example 1a), using a linear gradient of 20% A to 80% A over 25 min, then 80% A for 10 min, showed a single
5 peak at 14.92 min.

2b) the amide obtained under 2a) above (261 mg. 0.988 mmol) was added to a trifluoroacetic acid (TFA) / water solution (1:1, 6 ml). This solution was stirred at room temperature for 15 min, then the solvents were removed in vacuo. The residue was azeotroped with hexane (2 x 10 ml),
10 then recrystallised from ethyl acetate-hexane to give L-phenylalanine amide as it's TFA salt (202 mg. 73%). Analytical HPLC in the condition of example 2a), showed a single peak at 3.29 min.

2c) Diisopropylethylamine (233 ml. 1.34 mmol) was added at room temperature to a solution of the amide obtained under 2b) above (124 mg.
15 0.446 mmol), 2-methyl-2-(o-nitrophenoxy) propionic acid (103 mg. 0.457 mmol) and PyBOP (234 mg. 0.450 mmol) in DMF (2 ml). After 1h the solution was poured into water (15 ml) and the emulsion extracted with diethyl ether (30). The organic phase was washed with 5% NaHCO₃, water, 0.1N HCl, and brine, then dried (Na₂SO₄), filtered and the filtrate concentrated in
20 vacuo. The crude product was purified by column chromatography [SiO₂: 5% MeOH/ CHCl₃] to give the amide of N-(2-methyl-2(o-nitrophenoxy)propanoyl)L-phenylalanine (129 mg. 78%). Analytical HPLC in the condition of example 2a), showed a single peak TR = 17.74 min; TLC (5% MeOH/ CHCl₃) rf = 0.23.

25 2d) Bis (trifluoroacetoxy)iodobenzene (50 mg. 0.12 mmol) was dissolved in acetonitrile (4 ml), water (4 ml) was added followed by the amide obtained under 2c) above (43 mg. 0.12 mmol). After 3h at room temp. Analytical HPLC in the condition of example 2a) showed no starting

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material remained. The acetonitrile was removed in vacuo, and the residue treated with 4N HCl (30 ml, 0.12 mmol). The solution was concentrated in vacuo, and the residue triturated with ether to give hydrochloride of 1-(2-methyl-2(o-nitrophenoxy)propanoyl)amino-1-amino-2-phenylethane (42 mg, 5 91%) as a hygroscopic solid. Analytical HPLC in the condition of example 2a), showed a single peak TR = 17.32 min. No further purification was attempted.

2e) Diisopropylethylamine (239 ml, 1.37 mmol) was added to a mixture of phenylacetic acid (66 mg, 0.48 mmol), PyBOP (240 mg, 0.461 mmol), and the 10 amine obtained under 2d) above (174 mg, 0.458 mmol) in tetrahydrofuran (THF) (3 ml). The resulting yellow solution was stirred at room temp. for 7h. The THF was removed in vacuo, and the residue dissolved in ethyl acetate (100 ml). This solution was washed with 5% NaHCO₃ (25 ml), H₂O, 1N HCl (3 x 25 ml) and brine, then dried (Na₂SO₄), filtered and the 15 filtrate concentrated in vacuo. The crude product was purified by column chromatography [SiO₂: ethyl acetate-hexane 1:1] to give 1-(2-methyl-2(o-nitrophenoxy)propanoyl)amino-1-(phenylacetyl)amino-2-phenylethane (112 mg, 53%). Analytical HPLC in the condition of example 2a), showed a single peak TR= 23.50 min; TLC (5% MeOH/CHCl₃) rf = 0.66.

20 2f) Hydrogen gas was bubbled through a mixture of diamide obtained under 2e) above (110 mg, 0.238 mmol) and 10% Pd/carbon (11 mg) in acetic acid (2 ml), for 2 1/2 h. The mixture was filtered through Celite®, the filter aid was washed with acetic acid (3 x 3 ml), and the combined filtrate concentrated in vacuo. The residue was washed with cyclohexane (5 x 4 ml), the solid filtered and dried in vacuo, to give acetate of 1-amino-1-(phenylacetyl) amino-2-phenylethane (72 mg, 96%). Analytical HPLC in the 25 condition of example 2a), showed a single peak TR = 16.92 min (broad).

2g) WSC.HCl (55 mg, 0.29 mmol) was added to a chilled solution of cis N-

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(1(H)indol-3-yl-carbonyl)-2-aminocyclohexanecarboxylic acid (61 mg, 0.21 mmol) and HOBT (45 mg, 0.29 mmol) in THF (2 ml). The resulting solution was stirred at 0°C for 30 min, then a solution of acetate of 1-amino-1-(phenylacetyl) amino-2-phenylethane obtained under 2f) above (74 mg, 0.23 mmol) in THF (1 ml) was added, followed by dropwise addition of diisopropylethylamine (until pH 9). This solution was stirred at 0°C for 30 min, then at room temp. for 18h. The solvent was removed in vacuo and the residue dissolved in ethyl acetate (100 ml). The solution was washed with 1N HCl (2 x 25 ml), water, 5% NaHCO₃ (2 x 25 ml), water and brine, dried (Na₂SO₄), filtered and the filtrate concentrated in vacuo. The crude product was purified by preparative RP-HPLC, eluting with a gradient of 44% A to 64% A over 2h, to give the two diastereoisomers fast (12 mg, 11%) and slow (28 mg, 25%). HPLC analysis in the condition of example 2a), showed a single peak for each of the two products 15 (denominated "fast" and "slow" depending on their being eluted at an earlier or, respectively, at a later time):

HPLC (fast) = 22.48 min HPLC (slow) = 23.04 min

EXAMPLE 3

1-{N-(1(H)indol-3-yl-carbonyl)(1R,2S)-2-aminocyclohexanecarbonyl}-amino-
20 1-(N-methyl-N-phenylacetyl)amino-2(2-naphthyl)ethane and 1-{N-(1(H)indol-3-yl-carbonyl)(1S,2R)-2-aminocyclohexanecarbonyl}-amino-1-(N-methyl-N-phenylacetyl) amino-2(2-naphthyl)ethane

3a) Bis(trimethylsilyl)acetamide (1.84 ml, 7.46 mmol) was added, at room temp., to a suspension of D-3-(2-naphthyl)alanine (801 mg, 3.73 mmol) in 25 THF (8 ml). The mixture was stirred at room temp. until complete solution occurred (ca. 2h), then cooled to 0°C, and a solution of phenylacetic acid chloride (571 mg, 3.68 mmol) in THF (4 ml) added. The resulting solution was stirred at 0°C for 30 min. then at room temperature for 18h.

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Water (30 ml) was added, the mixture stirred for 20 min., then filtered. The solid was washed with H₂O and ethyl acetate, and the combined filtrate concentrated in vacuo to remove the organic solvents (a precipitate appeared). This solid was filtered, and air-dried to give N-5 (Phenylacetyl)-D-naphthylalanine (1.19 g, 96%); TLC (20% acetic acid/toluene) *rf* = 0.19; Analytical HPLC in the condition of example 2a), showed a single peak TR = 21.56 min; [a]D = -27.7° (c = 0.87, DMF).

3b) Sodium hydride (112 mg of an 80% dispersion in mineral oil), was added to a chilled solution of the product obtained under 3a) above (405 10 mg, 1.22 mmol) and methyl iodide (605 ml, 9.72 mmol) in THF (4 ml). The mixture was stirred at 0°C for 30 min., then at room temp. for 22h. The reaction was quenched by adding ethyl acetate (40 ml) and H₂O (10 ml). The layers were separated, and the organic phase extracted with 5% NaHCO₃ (20 ml). The combined aqueous extracts were cooled, acidified to pH 2 15 with 4N HCl, and extracted with ethyl acetate (100 ml). The organic phase was washed with 5% Na₂S₂O₃, H₂O and brine, then dried (Na₂SO₄), filtered and the filtrate concentrated in vacuo. The crude product was purified by preparative RP-HPLC, using a gradient system of 64% (H₂O + 0.1% TFA): 46% (CH₃CN + 0.1% TFA) to 44% A: 56% B over 2h, to give N-methyl-N-20 phenylacetyl-D-naphthylalanine (279 mg, 66%); TLC (20% acetic acid/toluene) *rf* = 0.29. Analytical HPLC in the condition of example 2a), isocratic elution with 52% A, showed a single peak TR = 10.31 min; [a]D = +49.8° (c = 1.01, DMF)

3c) WSC.HCl (104.5 mg, 0.544 mmol) was added to a chilled solution of 25 acid 3b (157.6 mg, 0.454 mmol) and the ammonium salt of HOBT (82.6 mg, 0.543 mmol) in DMF (2 ml). The solution was stirred at 0°C for 50 min, then at room temp. for 30 min. H₂O (20 ml) was added and the emulsion extracted with diethyl ether (200 ml). The organic phase was washed with

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5% NaHCO₃ (2 x 50 ml), H₂O, 1N HCl (2 x 50 ml), H₂O and brine, dried (Na₂SO₄), filtered, and the filtrate concentrated in vacuo. The crude product was purified by column chromatography [SiO₂: 8% MeOH/CHCl₃] to give N-methyl-N-phenylacetyl-D-naphthylalanine amide, (147 mg, 94%); TLC 5 (10% MeOH/CHCl₃) *rf* = 0.39. Analytical HPLC in the condition of example 2a), isocratic elution with 52% A, showed a single peak TR = 9.63 min; [a]D = +110° (c = 0.91, CHCl₃).

3d) Bis (260 mg, 0.606 mmol) was dissolved in CH₃CN (1.5 ml), H₂O (1.5 ml) was added, followed by amide 3c (133.4 mg, 0.386 mmol). The solution 10 was stirred at room temp. for 20 min, then diluted with H₂O (9 ml) and acidified with 1N HCl (9 ml). The emulsion was extracted with diethyl ether (30 ml), the layers separated, and the aqueous phase freeze-dried to give hydrochloride of 1-amino-1-(N-methyl-N-phenylacetyl) amino-2(2-naphthyl)ethane (93 mg, 68%), which was used the following step without 15 isolation.

3e) WSC.HCl (59.1 mg, 0.308 mmol) was added to a chilled solution of cis N-(1(H)indol-3-yl-carbonyl)-2-aminocyclohexan carboxylic acid (73.3 mg, 0.256 mmol) and HOEt (53.9 mg, 0.352 mmol) in CH₂Cl₂ (2 ml)/DMF (0.5 ml). The solution was stirred at 0°C for 30 min., amine hydrochloride 3d 20 (89 mg, 0.25 mmol) in CH₂Cl₂ (1 ml)/DMF (1 ml) was added, followed by dropwise addition of diisopropylethylamine (to pH 9). The reaction was stirred at 0°C for 30 min., then at room temp. for 18h. The CH₂Cl₂ was removed in vacuo, H₂O (10 ml) added, and the emulsion extracted with diethyl ether (100 ml). The layers were separated and the organic phase 25 washed with 1N HCl '2 x 25 ml), H₂O, 5% NaHCO₃ (2 x 25 ml), H₂O and brine, then dried (Na₂SO₄), filtered, and the filtrate concentrated in vacuo. The crude product was purified by preparative RP-HPLC in the condition of example 1a), eluting with a gradient of 55% A to 75% A over

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a period of 2h. to give diastereoisomer fast (44.1 mg, 30%); [HPLC (isocratic 65% A) TR = 9.36 min], and diastereoisomer slow (36.7 mg, 25%); [HPLC (isocratic 65% A) TR = 11.34 min].

Example 4

5 S-2-N(1(H)indol-3-yl-carbonyl)-(1R,2S)cis-2-aminocyclohexan-carboxamide)-1((3,5-bis(trifluoromethyl)phenyl)methyloxy)-3(2-naphthyl)propane and S-2-N(1(H)indol-3-yl-carbonyl)-(1S,2R)cis-2-aminocyclohexan-carboxamide)-1((3,5-bis(trifluoromethyl)phenyl)methyloxy)-3(2-naphthyl)propane.

4a) Lithium aluminium hydride in THF [1.0 M] (6.1 ml, 6.1 mmol) was added
10 dropwise to a chilled suspension of L-naphthylalanine (657 mg, 3.05 mmol)
in THF (3 ml). When the addition was complete the cooling bath was
removed and the mixture warmed to room temp. (vigorous gas evolution),
then for 1h, after which time TLC (Chloroform/methanol/acetic acid
85/10/5 V/V)) showed none of the amino acid remained. The mixture was
15 cooled to room temp. and quenched by cautiously adding H₂O (0.34 ml),
followed by 15% NaOH (0.34 ml) and H₂O (1 ml). The resulting mixture was
stirred at room temp. for 30 min., filtered, and the filtrate
concentrated in vacuo. The residue was partitioned between ethyl acetate
(50 ml) and 1N HCl (100 ml), the layers were separated, and the aqueous
phase basified to pH 10 with 10N NaOH. The aqueous phase was extracted
20 with ethyl acetate (2 x 100 ml), the layers separated, and the organic
phase washed with brine, dried (Na₂SO₄), filtered, and the filtrate
concentrated in vacuo to give amino alcohol (S)-2amino-
3(2naphthyl)propan-1-ol (443 mg, 72%); TLC (10% MeOH/CHCl₃) rf = 0.12.

25 4b) Diterbutyldicarbonate (127 mg, 0.582 mmol) was added to a solution
of amino alcohol 4a) (105 mg, 0.520 mmol) in CH₂Cl₂ (2 ml). The mixture
was stirred at room temperature for 18h, then the solvent was removed in
vacuo, and the residue purified by column chromatography [SiO₂: ethyl

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acetate-hexane 1:1] to give the (S)-2-(1,1-dimethyl-ethyloxycarbonyl)amino-3(2-naphthyl)propan-1-ol (112 mg, 71%); TLC (ethyl acetate-hexane 1:1) $rf = 0.35$.

4c) Triphenylphosphine (371 mg, 1.41 mmol) was added to a solution of 5 3,5-bistrifluoromethylbenzyl alcohol (257 mg, 1.05 mmol) in dry CCl_4 (2 ml). The mixture was refluxed for 1h, then cooled to room temp. Pentane (2 ml) was added, and the mixture stirred for a further 5 min., then filtered. The solid was washed with pentane (2 ml), and the filtrate concentrated in vacuo. The crude product was purified by column chromatography [SiO₂: hexane-ethyl acetate 4:1] to give 3,5-bistrifluoromethylbenzyl chloride (162 mg, 59%); TLC (hexane-ethyl acetate 1:1) $rf = 0.73$.

4d) Sodium hydride (15 mg of an 80% dispersion in mineral oil) was added to a solution of the product obtained under 4b) above (110.3 mg, 0.366 mmol) in DMF (1 ml) at -10°C. The mixture was stirred at -10°C for 10 min., chloride 4c) (147 mg, 0.560 mmol) in DMF (1 ml) was added, and the stirring continued at -10°C for 15 min, then at room temp. for 4h. Saturated NH₄Cl (2 ml) was added, the solution diluted with H₂O (20 ml), and extracted with ethyl acetate (2 x 50 ml). The organic extract was 20 dried (Na₂SO₄), filtered, and the filtrate concentrated in vacuo. The crude product was purified by column chromatography [SiO₂: hexane-ethyl acetate 3:1] to give (S)-2-(1,1-dimethyl-ethyloxycarbonyl)amino-1-((3,5-bis(trifluoromethyl)methoxy)-3(2-naphthyl)propane (135 mg, 70%); TLC (hexane-ethyl acetate 2:1) $rf = 0.66$

25 4e) A saturated solution of HCl in ethyl acetate (2 ml) was added dropwise to a chilled solution of ether 4d) (118 mg, 0.224 mmol) in CH₂Cl₂ (2 ml). The cooling bath was removed and the solution stirred at room temp. for 1h (a precipitate appeared). The excess HCl was removed by

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bubbling N₂ through the mixture, the solid was filtered, washed with hexane, and air-dried to give (S)-2-amino-1-((3,5-bis(trifluoromethyl)methoxy)-3(2-naphthyl)propane hydrochloride (85.7 mg, 82%); TLC (CMA) *rf* = 0.36

5 4f) WSC.HCl (42.6 mg, 0.222 mmol) was added to a chilled solution of acid cis N-(1(H)indol-3-yl-carbonyl)-2-aminocyclohexanecarboxylic acid (53.5 mg, 0.187 mmol) and HOBT (32.3 mg, 0.211 mmol) in CH₂Cl₂(1 ml)/DMF (0.25 ml). The solution was stirred at 0°C for 25 min., the product obtained under 4b) above (81.9 mg, 0.177 mmol) was added, followed by dropwise
10 addition of diisopropylethylamine (to pH 9). Stirring was continued at 0°C for 30 min. then at room temp. for 18h. The CH₂Cl₂ was removed in vacuo, H₂O (10 ml) was added, and the emulsion extracted with diethyl ether (50 ml). The layers were separated, the organic phase was washed with 1N HCl (2 x 25 ml), H₂O, 5% NaHCO₃ (2 x 25 ml), H₂O, and brine,
15 dried (Na₂SO₄), filtered, and the filtrate concentrated in vacuo. The crude product was purified by preparative RP-HPLC, eluting with a gradient of 25% A (H₂O + 0.1% TFA): 75% B (methanol) to 5% A: 95% B over a period of 2h. to give diastereoisomer fast (50.6 mg, 41%); HPLC (isocratic 88% B) TR = 8.40 min., and diastereoisomer slow (50.3 mg,
20 41%); HPLC (isocratic 88% B) TR = 9.46 min.

Following the procedures described in Examples 1-4, these compounds were also obtained:

5) 1-{N-(1(H)indol-3-yl-carbonyl)(1R,2S)-2-aminocyclohexanecarbonyl}-
amino-1-N(phenylacetyl)amino-2(2-naphthyl)ethane and 1-{N-(1(H)indol-3-
25 yl-carbonyl) (1S,2R)-2-aminocyclohexanecarbonyl}-amino-1-N(phenylacetyl)
amino-2(2-naphthyl)ethane

HPLC: column Phase Sep. Spherisorb ODS-2 5mm (250x4.6) fitted with a Phase Sep. Spherisorb S5 ODS-2 (50x4.6 mm) precolumn; eluent A: H₂O, 0.1%

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trifluoroacetic acid; eluent B:

Acetonitrile, 0.1% trifluoroacetic acid; UV Detection 215 nm; flow 1 ml/min; linear gradient from 20% to 80% B in 20 min, then isocratic 80% B for 10 min (HPLC System 1):

5 fast: TR = 24.55 min slow TR = 25.07 min;

TLC(SiO₂)CHCl₃/CH₃OH (9:1 v/v) R_f = 0.37 and 0.40

6) 1-{N-(1(H)indol-3-yl-carbonyl)(1R,2S)-2-aminocyclohexanecarbonyl}-amino-1-(N-methyl-N-phenylacetyl)amino-2-phenylethane and 1-{N-(1(H)indol-3-yl-carbonyl) (1S,2R)-2-aminocyclohexanecarbonyl}-amino-1-(N-methyl-N-phenylacetyl)amino-2-phenylethane
10

HPLC: (System 1)

fast: TR = 23.4 min slow TR = 24.5 min;

TLC(SiO₂)CHCl₃/CH₃OH (90:10 v/v) R_f = 0.67 and 0.84

7) 1-{N-(1(H)indol-3-yl-carbonyl)(1R,2S)-2-aminocyclohexanecarbonyl}-amino-1-(N-methyl-N((2-naphthyl)acetyl))amino-2-phenylethane and 1-{N-(1(H)indol-3-yl-carbonyl) (1S,2R)-2-aminocyclohexanecarbonyl}-amino-1-(N-methyl-N((2-naphthyl)acetyl)) amino-2-phenylethane
15

HPLC: column Phase Sep. Spherisorb ODS-2 5 mm (250 x 4.6 mm)

fitted with a Phase Sep. Spherisorb S5 ODS-2 (50 x 4.6 mm)

20 precolumn; eluent A: H₂O, 0.1% trifluoroacetic acid; eluent B:

Acetonitrile, 0.1% trifluoroacetic acid; UV Detection 215 nm; flow 1 ml/min; (HPLC system 2) isocratic 70% B;

fast: TR = 4.83 min slow TR = 5.74 min;

8) 1-{N-(1(H)indol-3-yl-methyl)(1R,2S)-2-aminocyclohexanecarbonyl}-amino-1-N(phenylacetyl)amino-2(2-naphthyl)ethane and 1-{N-(1(H)indol-3-yl-methyl) (1S,2R)-2-aminocyclohexanecarbonyl}-amino-1-N(phenylacetyl)amino-2(2-naphthyl)ethane
25

HPLC: (System 1) fast: TR = 21.36 min slow TR = 22.42 min;

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TLC(SiO₂) CHCl₃/CH₃OH (95:5 v/v) R_f = 0.15 and 0.17

9) 1-{N-(1(H)indol-3-yl-carbonyl)(1R,2S)-2-aminocyclohexanecarbonyl}-amino-1-(N-methyl-N-((S)2-phenylpropionyl))amino-2-(2-naphthyl)ethane and 1-{N-(1(H)indol-3-yl-carbonyl)} (1S,2R)-2-aminocyclohexanecarbonyl}-amino-5 1-(N-methyl-N-((S)2-phenylpropionyl)) amino-2-(2-naphthyl)ethane

HPLC:(System 1) fast: TR = 27.04 min slow TR = 27.42 min;

TLC(SiO₂) CHCl₃/CH₃OH (95:5 v/v) R_f = 0.26 and 0.26

10) 1-{N-(1(H)indol-3-yl-carbonyl)(1R,2S)-2-aminocyclohexane-carbonyl}-amino-1-(N-methyl-N-((R)2-phenylpropionyl))amino-2-(2-naphthyl)ethane and 1-{N-(1(H)indol-3-yl-carbonyl)} (1S,2R)-2-aminocyclohexanecarbonyl}-amino-1-(N-methyl-N-((R)2-phenylpropionyl)) amino-2-(2-naphthyl)ethane

HPLC:(System 2) isocratic 65% B

fast: TR = 12.14 min slow TR = 16.5 min;

15 11) 1-{N-(1(H)indol-3-yl-carbonyl)(1R,2S)-2-aminocyclohexanecarbonyl}-amino-1-(N-methyl-N-4-chlorophenylacetyl)amino-2(2-naphthyl)ethane and 1-{N-(1(H)indol-3-yl-carbonyl)(1S,2R)-2-aminocyclohexanecarbonyl}-amino-1-(N-methyl-N-4-chlorophenylacetyl) amino-2(2-naphthyl)ethane

HPLC: (System 1)

20 fast: TR = 27.7 min slow TR = 28.8 min;

12) 1-{N-(1(H)indol-3-yl-carbonyl)(1R,2S)-2-aminocyclohexanecarbonyl}-amino-1-(N-methyl-N-4-methylphenylacetyl)amino-2(2-naphthyl)ethane and 1-{N-(1(H)indol-3-yl-carbonyl)(1S,2R)-2-aminocyclohexanecarbonyl}-amino-1-(N-methyl-N-4-methylphenylacetyl) amino-2(2-naphthyl)ethane

25 HPLC: System 1)

fast: TR = 27.7 min slow TR = 28.94 min;

13) 1-N-[N(benzoyl)-(R,S)cis-2-amino-cyclohexane-carbonyl]-amino-1-[N(methyl)N(phenylacetyl)]amino-2(2-naphthyl)ethane and 1-N-[N(benzoyl)-

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(S,R)cis-2-amino-ciclohexane-carbonyl]-amino-1-[N(methyl)N(phenylacetyl)]amino-2(2-naphthyl)ethane

14) 1-N-[N(4-methyl-benzoyl)-(R,S)cis-2-amino-ciclohexane-carbonyl]-amino-1-[N(methyl)N(phenylacetil)]amino-2(2-naphthyl)ethane and 1-N-[N(4-methyl-benzoil)-(S,R)cis-2-amino-cyclohexane-carbonyl]amino-1-[N(methyl)N(phenylacetil)]amino-2(2-naphthyl)ethane 15) 1-N-[N(4-metossi-benzoil)-(R,S)cis-2-amino-cyclohexane-carbonyl]-amino-1-[N(methyl)N(phenylacetil)]amino-2(2-naphthyl)ethane and 1-N-[N(4-metossi-benzoil)-(S,R)cis-2-amino-cyclohexane-carbonyl]amino-1-[N(methyl)N(phenylacetil)]-amino-2(2-naphthyl)ethane

10 16) 1-N-[N(4-cloro-benzoil)-(R,S)cis-2-amino-cyclohexane-carbonyl]-amino-1-[N(methyl)N(phenylacetil)]amino-2(2-naphthyl)ethane and 1-N-[N(4-cloro-benzoil)-(S,R)cis-2-amino-cyclohexane-carbonyl]amino-1-[N(methyl)N(phenylacetil)]amino-2(2-naphthyl)ethane

17) 1-N-[N(3,4-cloro-benzoil)-(R,S)cis-2-amino-cyclohexane-carbonyl]-amino-1-[N(methyl)N(phenylacetil)]amino-2(2-naphthyl)ethane and 1-N-[N(3,4-cloro-benzoil)-(S,R)cis-2-amino-cyclohexane-carbonyl]amino-1-[N(methyl)N(phenylacetil)]amino-2(2-naphthyl)ethane

18) 1-N-[N(1(Methyl)indol-3-yl-carbonyl)-(R,S)cis-2-amino-cyclohexane-carbonyl]-amino-1-[N(methyl)N(phenylacetil)]amino-2(2-naphthyl)ethane

20 and 1-N-[N(1(methyl)indol-3-yl-carbonyl)-(S,R)cis-2-amino-cyclohexane-carbonyl]amino-1-[N(methyl)N(phenylacetil)]amino-2(2-naphthyl)ethane

19) 1-N-[N(1(methyl)indol-3-yl-carbonyl)-N-methyl-(R,S)cis-2-amino-cyclohexane-carbonyl]-amino-1-[N(methyl)N(phenylacetil)]amino-2(2-naphthyl)ethane and 1-N-[N(1(methyl)indol-3-yl-carbonyl)-N-methyl-(S,R)cis-2-amino-cyclohexane-carbonyl]amino-1-[N(methyl)N(phenylacetil)]amino-2(2-naphthyl)ethane

25 20) 1-N-[N(1(H)indol-3-yl-carbonyl)-(R,S)cis-2-amino-cyclohexane-

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carbonyl]-amino-1-[N(methyl)N(phenylacetil)]amino-2(p-metossi)phenylethane and 1-N-[N(1(H)indol-3-yl-carbonyl)-(S,R)cis-2-amino-cyclohexane-carbonyl]amino-1-[N(methyl)N(phenylacetil)]amino-2(p-metossi)phenylethane

5 21) N-[N(1(Methyl)indol-3-yl-carbonyl)-N-methyl-(R,S)cis-2-amino-cyclohexane-carbonyl]-2-naphthylalanine N-methyl-N-benzilamide and N[N(1(methyl)indol-3-yl-carbonyl)-N-methyl-(S,R)cis-2-amino-cyclohexane-carbonyl]-2-naphthylalanine-N-methyl-N-benzilamide.

Assessment of biological activity (antagonist activity on NK1 receptor) of compounds of this invention was performed by means of the following binding and functional assays:

[3H] SP binding assay in IM9 Cell Line

Binding assay was performed with intact cells as described by Goso et al (Eur.J.Pharmacol. 254, 221, 1994).

15 Measurement of pA2 in isolated guinea pig ileum

Male albino guinea-pigs weighing 300-350 g were stunned and bled. A segment of ileum was excised and placed in oxygenated Krebs solution containing 10 mM indomethacin. After 90 min. equilibration period a cumulative concentration-response curve for the agonist, [Sar9] substance P sulfone was made. After two or more reproducible control curves for the agonist had been obtained, the compound to be tested was added to the bath and a new curve for the agonist was determined in its presence. pA2 values were calculated by using the constrained Schild plot method.

The data in Table I were obtained for compound of formula (I):

- 25 -

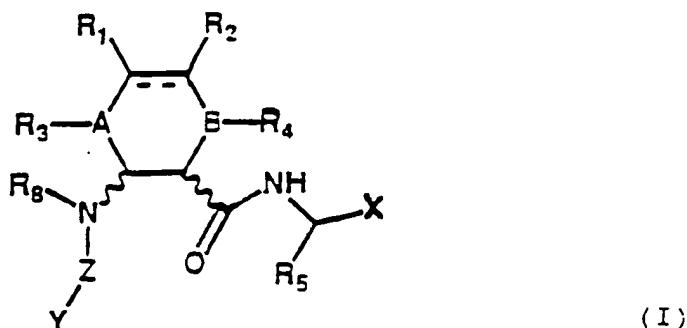
Table I

Substance P antagonism Results

Compounds	pKi
1 (fast)	<6
2 (fast)	<6
3 (fast)	8.4
3 (slow)	<5
4 (fast)	<5
9 (fast)	<5
10 (fast)	8.7
11 (fast)	8.4
12 (fast)	8.7

CLAIMS

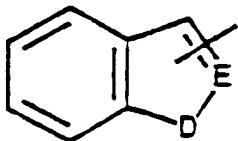
1 1. Compounds having general formula (I)



3 wherein:

4 Y is selected out of a group consisting of an aryl-, aryl-alkyl-, alkyl-
 5 aryl- radical containing 7 to 12 carbon atoms, whose aromatic ring
 6 possibly contains an heteroatom selected from the group N,O,S, and
 7 wherein the aromatic ring is unsubstituted or substituted with one or
 8 more substituent(s) selected from a group consisting of halogen, a linear
 9 or branched alkyl radical containing 1 to 6 carbon atoms, possibly
 10 substituted with not more than three fluorine atoms, a linear or branched
 11 oxyalkyl radical containing not more than three fluorine atoms, -NH₂, -
 12 NHR₁₁, -N(R₁₁)₂, -CONHR₁₁, -COR₁₁, -COOR₁₁, -R₁₂COOR₁₁, -CONHR₁₁, -
 13 R₁₂CONHR₁₁, -NHCOR₁₁, -NHCOOR₁₁, -R₁₂COOR₁₁, nitro, wherein R₁₁ and R₁₂
 14 are independently selected from H, a linear or branched alkyl radical
 15 containing 1 to 6 carbon atoms, a radical of type

- 27 -



16 wherein D stands for O, S, CH₂, N-R₉ where R₉ is selected from a group
17 consisting of H, a linear or branched alkyl radical containing 1 to 6
18 carbon atoms, acyl radical R₁₀-CO wherein R₁₀ is selected from H, a
19 linear or branched alkyl radical containing 1 to 3 carbon atoms and E =
20 CH or N, each with suitable substituents;

21 Z is selected from the group consisting of CH₂ and CO;

22 R₈ is selected from a group consisting of H, a linear or branched alkyl
23 radical containing 1 to 6 carbon atoms;

24 symbol — represents a single or a double bond: if the bond is single,
25 R₁ and R₂ are selected out of a group consisting of hydrogen, hydroxyl,
26 methoxyethoxyethoxyl or methoxyethoxymethoxyl, and halogen or are joined
27 to form an epoxide; if the bond is double, they are hydrogen or halogen;

28 A and B stand for N or CH; R₃ and R₄ are selected out of the group
29 consisting of hydrogen, a linear or branched alkyl radical containing 1
30 to 6 carbon atoms, or are joined together to form a -(CH₂)_n- bridge,
31 where n stands for a whole number from 1 to 3;

32 R₅ is selected out of a group consisting of an aryl-, aryl-alkyl-, alkyl-
33 aryl- radical containing up to 15 carbon atoms, whose aromatic ring
34 possibly contains an heteroatom selected from the group N,O,S, and
35 wherein the aromatic ring is unsubstituted or substituted with one or
36 more substituent(s) selected from a group consisting of halogen, a linear

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37 or branched alkyl radical containing 1 to 6 carbon atoms, possibly
38 substituted with not more than three fluorine atoms, a linear or branched
39 oxyalkyl radical containing not more than three fluorine atoms, -NH₂, -
40 NHR₁₁, -N(R₁₁)₂, -CONHR₁₁, -COR₁₁, -COOR₁₁, -R₁₂COOR₁₁, -CONHR₁₁, -
41 R₁₂CONHR₁₁, -NHCOR₁₁, -NHCOOR₁₁, -R₁₂COOR₁₁, nitro, wherein R₁₁ and R₁₂
42 are as defined above;

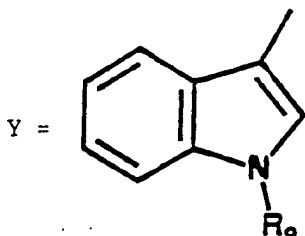
43 X is selected from a group consisting of COOR₆, -CH₂OR₆, -NR₇COR₆, -
44 NR₆COOR₇, -CONR₆R₇. R₆ and R₇ are independently selected out of a group
45 consisting of an aryl-, aryl-alkyl-, alkyl-aryl- radical containing up to
46 15 carbon atoms, whose aromatic ring possibly contains an heteroatom
47 selected from the group N,O,S, and wherein the aromatic ring is
48 unsubstituted or substituted with one or more substituent(s) selected
49 from a group consisting of halogen, a linear or branched alkyl radical
50 containing 1 to 6 carbon atoms, possibly substituted with not more than
51 three fluorine atoms, a linear or branched oxyalkyl radical containing
52 not more than three fluorine atoms, -NH₂, -NHR₁₁, -N(R₁₁)₂, -CONHR₁₁, -
53 COR₁₁, -COOR₁₁, -R₁₂COOR₁₁, -CONHR₁₁, -R₁₂CONHR₁₁, -NHCOR₁₁, -NHCOOR₁₁, -
54 R₁₂COOR₁₁, nitro, wherein R₁₁ and R₁₂ are as defined above, with the
55 proviso that if X= -CONR₆R₇ then Z is other than CO or R₈ is other than
56 H.

55 Symbol ~~~ means that the configuration of those asymmetric carbon
56 atoms of 2-amino-cyclohexanecarboxylic acid could be either S or R, with
57 the proviso that such configuration can not be S or R for both the
58 asymmetric carbon atoms (the two substituents must be cis).

1 2. The compound according to claim 1, wherein

2

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- 1 3. The compound according to claim 2, wherein $Z = CO$; $R8 = H$, $X = -$
- 2 NR_7COR_6
- 3 and $R1, R2, R3, R^4, R5, R6, R7, R9, R10, R11, A$, and B are as defined
- 4 above.
- 1 4. The compound according to claim 3, wherein the alkyl radical is
- 2 selected out of the group consisting of methyl, ethyl, propyl, butyl, and
- 3 pentyl; the alkynyl radical is propynyl; aryl-alkyl-aryl- and aryl-
- 4 alkyl-radicals present an alkyl radical as defined above, while the aryl
- 5 moiety is selected out of the group consisting of possibly substituted
- 6 pyridine, benzofuran, benzene, indole, naphthyl, tetrahydroquinoline,
- 7 imidazole, tetrahydroindoline;
- 1 5. Compounds of formula (I) represented by:
- 2 1) benzyl ester of $N^{\alpha}-\{[N(1(H)indol-3-yl-carbonyl)(1R,2S)-2-$
- 3 aminocyclohexan carbonyl}-L-phenylalanine and benzyl ester of $N^{\alpha}-$
- 4 $\{[1(H)N(indol-3-yl-carbonyl)(1S,2R) 2-aminocyclohexancarbonyl]-L-$
- 5 phenylalanine
- 6 2) $1-\{N-(1(H)indol-3-yl-carbonyl)(1R,2S)-2-aminocyclohexanecarbonyl\}-$
- 7 amino-1-(phenylacetyl)amino-2-phenyl-ethane and $1-\{N-(1(H)indol-3-yl-$
- 8 carbonyl)(1S,2R)-2-aminocyclohexanecarbonyl}-amino-1-(phenylacetyl)
- 9 amino-2-phenyl-ethane
- 10 3) $1-\{N-(1(H)indol-3-yl-carbonyl)(1R,2S)-2-aminocyclohexanecarbonyl\}-$
- 11 amino-1-(N-methyl-N-phenylacetyl)amino-2(2-naphthyl)ethane and $1-\{N-$
- 12 $(1(H)indol-3-yl-carbonyl)(1S,2R)-2-aminocyclohexanecarbonyl\}-amino-1-(N-$
- 13 methyl-N-phenylacetyl) amino-2(2-naphthyl)ethane

- 30 -

14 4) S-2-N(1(H)indol-3-yl-carbonyl)-(1R,2S)cis-2-aminocyclohexan-
15 carboxamide)-1((3,5-bis(trifluoromethyl)phenyl)methyloxy)-3(2-
16 naphthyl)propane and S-2-N(1(H)indol-3-yl-carbonyl)-(1S,2R)cis-2-
17 aminocyclohexan-carboxamide)-1((3,5-bis(trifluoromethyl)phenyl)
18 methyloxy)-3(2-naphthyl)propane
19 5)1-{N-(1(H)indol-3-yl-carbonyl)(1R,2S)-2-aminocyclohexanecarbonyl}-
20 amino-1-N(phenylacetyl)amino-2(2-naphthyl)ethane and 1-{N-(1(H)indol-3-
21 yl-carbonyl) (1S,2R)-2-aminocyclohexanecarbonyl}-amino-1-N(phenylacetyl)
22 amino-2(2-naphthyl)ethane
23 6) 1-{N-(1(H)indol-3-yl-carbonyl)(1R,2S)-2-aminocyclohexanecarbonyl}-
24 amino-1-(N-methyl-N-phenylacetyl)amino-2-phenylethane and 1-{N-
25 (1(H)indol-3-yl-carbonyl) (1S,2R)-2-aminocyclohexanecarbonyl}-amino-1-(N-
26 methyl-N-phenylacetyl)amino-2-phenylethane
27 7) 1-{N-(1(H)indol-3-yl-carbonyl)(1R,2S)-2-aminocyclohexanecarbonyl}-
28 amino-1-(N-methyl-N((2-naphthyl)acetyl))amino-2-phenylethane and 1-{N-
29 (1(H)indol-3-yl-carbonyl) (1S,2R)-2-aminocyclohexanecarbonyl}-amino-1-(N-
30 methyl-N((2-naphthyl)acetyl))amino-2-phenylethane
31 8) 1-{N-(1(H)indol-3-yl-methyl)(1R,2S)-2-aminocyclohexanecarbonyl}-
32 amino-1-N(phenylacetyl)amino-2(2-naphthyl)ethane and 1-{N-(1(H)indol-3-
33 yl-methyl) (1S,2R)-2-aminocyclohexanecarbonyl}-amino-1-
34 N(phenylacetyl)amino-2(2-naphthyl)ethane
35 9) 1-{N-(1(H)indol-3-yl-carbonyl)(1R,2S)-2-aminocyclohexanecarbonyl}-
36 amino-1-(N-methyl-N-((S)2-phenylpropionyl))amino-2-(2-naphthyl)ethane
37 and 1-{N-(1(H)indol-3-yl-carbonyl) (1S,2R)-2-aminocyclohexanecarbonyl}-
38 amino-1-(N-methyl-N-((S)2-phenylpropionyl)) amino-2-(2-naphthyl)ethane
39 10)1-{N-(1(H)indol-3-yl-carbonyl)(1R,2S)-2-aminocyclohexanecarbonyl}-
40 amino-1-(N-methyl-N-((R)2-phenylpropionyl))amino-2-(2-naphthyl)ethane
41 and 1-{N-(1(H)indol-3-yl-carbonyl) (1S,2R)-2-aminocyclohexanecarbonyl}

42 -amino-1-(N-methyl-N-((R)2-phenylpropionyl)) amino-2-(2-naphthyl)ethane
43 11) 1-{N-(1(H)indol-3-yl-carbonyl)(1R,2S)-2-aminocyclohexanecarbonyl}-
44 amino-1-(N-methyl-N-4-chlorophenylacetyl)amino-2(2-naphthyl)ethane and 1-
45 {N-(1(H)indol-3-yl-carbonyl)(1S,2R)-2-aminocyclohexanecarbonyl}-
46 amino-1-(N-methyl-N-4-chlorophenylacetyl) amino-2(2-naphthyl)ethane
47 12) 1-{N-(1(H)indol-3-yl-carbonyl)(1R,2S)-2-aminocyclohexanecarbonyl}-
48 amino-1-(N-methyl-N-4-methylphenylacetyl)amino-2(2-naphthyl)ethane
49 and 1-{N-(1(H)indol-3-yl-carbonyl)(1S,2R)-2-aminocyclohexanecarbonyl}-
50 amino-1-(N-methyl-N-4-methylphenylacetyl) amino-2(2-naphthyl)ethane
51 13)1-N-[N(benzoyl)-(R,S)cis-2-amino-ciclohexane-carbonyl]-amino-1-
52 [N(methyl)N(phenylacetyl)]amino-2(2-naphthyl)ethane and 1-N-[N(benzoyl)-
53 (S,R)cis-2-amino-ciclohexane-carbonyl]-amino-1-[N(methyl)
54 N(phenylacetyl)]amino-2(2-naphthyl)ethane
55 14)1-N-[N(4-methyl-benzoyl)-(R,S)cis-2-amino-ciclohexane-carbonyl]-amino-
56 1-[N(methyl)N(phenylacetil)]amino-2(2-naphthyl)ethane and 1-N-[N(4-
57 methyl-benzoil)-(S,R)cis-2-amino-cyclohexane-carbonyl]amino-1-
58 [N(methyl)N(phenylacetil)]amino-2(2-naphthyl)ethane
59 15)1-N-[N(4-metossi-benzoil)-(R,S)cis-2-amino-cyclohexane-carbonyl]-
60 amino-1-[N(methyl)N(phenylacetil)]amino-2(2-naphthyl)ethane and 1-N-[N(4-
61 metossi-benzoil)-(S,R)cis-2-amino-cyclohexane-carbonyl]amino-1-
62 [N(methyl)N(phenylacetil)]amino-2(2-naphthyl)ethane
63 16)1-N-[N(4-cloro-benzoil)-(R,S)cis-2-amino-cyclohexane-carbonyl]-amino-
64 1-[N(methyl)N(phenylacetil)]amino-2(2-naphthyl)ethane and 1-N-[N(4-cloro-
65 benzoil)-(S,R)cis-2-amino-cyclohexane-carbonyl]amino-1-
66 [N(methyl)N(phenylacetil)]amino-2(2-naphthyl)ethane
67 17)1-N-[N(3,4-cloro-benzoil)-(R,S)cis-2-amino-cyclohexane-carbonyl]-
68 amino-1-[N(methyl)N(phenylacetil)]amino-2(2-naphthyl)ethane and 1-N-
69 [N(3,4-cloro-benzoil)-(S,R)cis-2-amino-cyclohexane-carbonyl]amino-1-

70 [N(methyl)N(phenylacetil)]amino-2(2-naphthyl)ethane
71 18)1-N-[N(1(Methyl)indol-3-yl-carbonyl)-(R,S)cis-2-amino-cyclohexane-
72 carbonyl] -amino-1-[N(methyl)N(phenylacetil)]amino-2(2-naphthyl)ethane
73 and 1-N[N(1(methyl)indol-3-yl-carbonyl)-(S,R)cis-2-amino-cyclohexane-
74 carbonyl]amino-1-[N(methyl)N(phenylacetil)]amino-2(2-naphthyl)ethane
75 19)1-N-[N(1(methyl)indol-3-yl-carbonyl)-N-methyl-(R,S)cis-2-amino-
76 cyclohexane-carbonyl]-amino-1-[N(methyl)N(phenylacetil)]amino-2 (2-
77 naphthyl)ethane and 1-N-[N(1(methyl)indol-3-yl-carbonyl)-N-methyl-
78 (S.R)cis-2-amino-cyclohexane-carbonyl]amino-1-[N(methyl)N
79 (phenylacetil)]amino-2 -(2-naphthyl)ethane
80 20)1-N-[N(1(H)indol-3-yl-carbonyl)-(R,S)cis-2-amino-cyclohexane-
81 carbonyl]-amino-1-[N(methyl)N(phenylacetil)]amino-2(pmetossi)
82 phenylethane and 1-N-[N(1(H)indol-3-yl-carbonyl)-(S,R)cis-2-amino-
83 cyclohexane-carbonyl]amino-1-[N(methyl)N(phenylacetil)]amino-2
84 (p-metossi)phenylethane
85 21)N-[N(1(Methyl)indol-3-yl-carbonyl)-N-methyl-(R,S)cis-2-amino-
86 cyclohexane-carbonyl]-2-naphthylalanine N-methyl-N-benzilamide and
87 N[N(1(methyl)indol-3-yl-carbonyl)-N-methyl-(S,R)cis-2-amino-cyclohexane-
88 carbonyl]-2-naphthylalanine-N-methyl-N-benzilamide.

1 6. Pharmaceutical composition containing, as active ingredient, an
2 effective dose of compound as per formula (I) according to claim 1.

1 7. Pharmaceutical composition containing, as active ingredient, an
2 effective dose of compound according to claim 2.

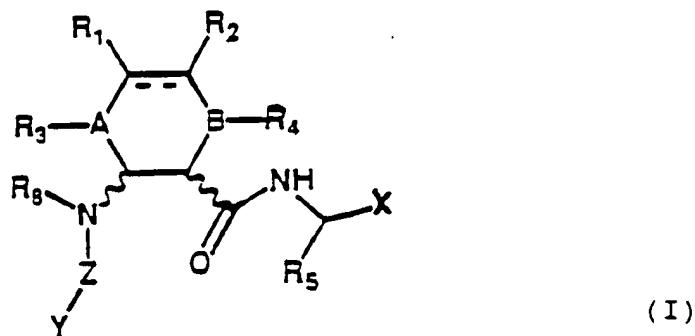
1 8. Pharmaceutical composition containing, as active ingredient, an
2 effective dose of compound according to claim 3.

1 9. Use of compounds of formula (I) according to claims 1, 2, 3, and 4, as
2 active ingredients for the preparation of pharmaceutical compositions.

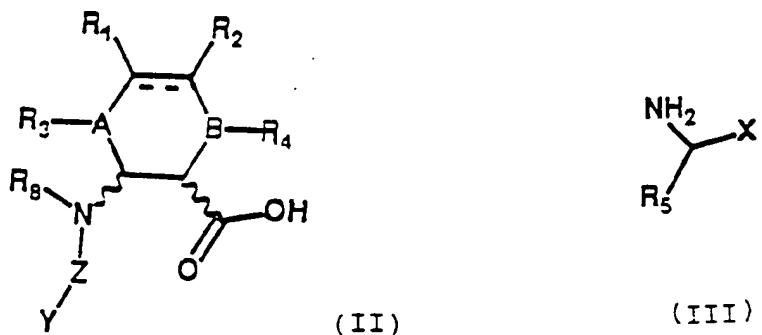
1 10. Process for the preparation of tachykinin antagonist compound having

- 33 -

2 general formula (I)

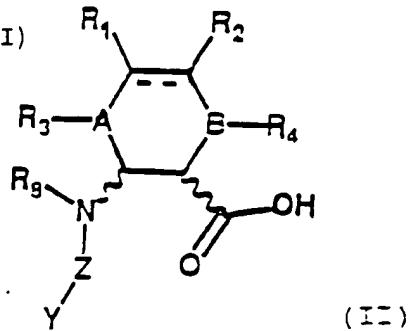


3 condensing, in the presence of a suitable condensing agent, intermediate
4 of formula (II) with intermediate of formula (III)



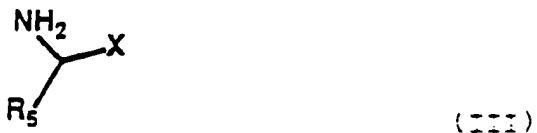
5 wherein R1, R2, R3, R4, R5, R6, R7, R8, R9, R10, R11, A, B, Z, X, Y are
6 as defined above.

1 11. Compounds of general formula (II)



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2 wherein R₁, R₂, R₃, R₄, R₈, A, B, Y are as defined in claim 1, Z= CH₂,
3 R₈=H, and with the proviso that X is not CONR₆R₇.
1 12. Compounds of general formula (III)



2 wherein R₅ and X are as defined in claim 1.
1 13. Process for the preparation of compounds of general formula (II)
2 according to claim 11 as described in scheme 1.
1 14. Process for the preparation of compounds of general formula (III)
2 according to claim 12 as described in scheme 2.

INTERNATIONAL SEARCH REPORT

Int. Application No

PCT/EP 94/04012

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 6 C07D209/42 A61K31/40 C07D209/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
 IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO,A,91 18899 (PFIZER INC.) 12 December 1991 see claims ---	1,6
A	JOURNAL OF MEDICINAL CHEMISTRY, vol.36, 6 August 1993, WASHINGTON US pages 2266 - 2278 DAIJIRO HAGIWARA ET AL. 'Studies on neurokinin antagonists. 3. Design and structure-activity relation ships of new branched tripeptides ...' * page 2266-2267 *	1,6
P,X	WO,A,94 13694 (A. MENARINI INDUSTRIE FARMACEUTICHE REUNITE S.R.L.) 23 June 1994 cited in the application * complete document * -----	1,6

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

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1 Date of the actual completion of the international search

Date of mailing of the international search report

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Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

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INTERNATIONAL SEARCH REPORT

...information on patent family members

Internat'l Application No

PCT/EP 94/04012

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		AU-A-	7860291	31-12-91
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WO-A-9413694	23-06-94	AU-B-	5650894	04-07-94
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